REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Claim Amendments

Claims 41, 66 and 80-82 have been amended to remove the reference to a tissue-specific or target-specific promoter. Consistent with these amendments, claim 58 has been amended to recite a tissue-specific promoter, and claim 59 has been amended to recite the particular tissue-specific promoter previously included in claim 58.

Claims 41, 66 and 80-82 have also been amended to recite "wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue." Support for this recitation can be found, for example, at page 39, line 13 to page 40, line 19.

Claim 82 has been additionally amended to correct a typographical error by deleting "b)" from before the recitation "cis acting polynucleotide sequence," and changing "c)" to "b)".

New claims 83-86 have been added. Support for these new claims can be found, for example, in the original claim 1 and at page 45, lines 8-24 of the specification.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Double Patenting (Pages 2-13 of the Office Action)

Various claims of the present application stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the claims of U.S. Patent No. 6,899,871. An appropriate terminal disclaimer will be submitted in due course to overcome these rejections.

Rejections Under 35 U.S.C. §112, Enablement (Pages 13-28 of the Office Action)

The rejection of claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75 and 77-82 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement, is respectfully traversed for the reasons set forth below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. MPEP §2164.01; *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Claim 41, a representative claim in the present application, is directed to a method of treating a subject having a cell proliferative disorder comprising:

a) contacting the subject with a therapeutically effective amount of a retrovirus, comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' and 3' end of the retroviral genome;

a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell,

in a pharmaceutically acceptable carrier; and

b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;
wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

Thus, the claimed invention relates to treating certain cell proliferative disorders using a retrovirus as specified in the claims. The Office Action alleges that undue experimentation would be necessary to practice the claimed invention. In particular, the Office Action specifically asserts that in order to practice the claimed invention in vivo, a number of variables would have to be optimized, including: (i) the mode of delivery of retroviral factors to an organism that would allow it to reach the targeted cell, (ii) the amount of retroviral vector that would need to be delivered in order to express a stable and sufficient amount of the therapeutic gene for prevention or treatment once it reaches the cell, (iii) ensuring that the nucleic acid remains viable in a cell for a period of time that allows expression to an extent that there is a measurable and significant therapeutic effect, and (iv) overcoming drug resistance. For the reasons set forth below, Applicants respectfully disagree.

A declaration by Dr. Noriyuki Kasahara under 37 C.F.R. §1.132 accompanies the present response. The declaration describes the manner in which one skilled in the art of gene therapy can use the method of the invention, according to the disclosure of the present application and knowledge in the art, to treat a cell proliferative disorder. Specifically, the declaration provides data that clearly indicate the claimed method can be used to treat a cell proliferative disorder (e.g., glioblastoma). The vector employed in the treatment were constructed and used as disclosed in the specification. Thus, the declaration provides data that indicate that a therapeutic effect can be achieved by the methods and vectors described in the specification; i.e., that delivery of a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug to a subject provides a therapeutic effect.

The data were obtained from experiments using animal models typically used in gene therapy research. Applicants submit that the Training Materials for Examining Patent applications, with

respect to enablement for chemical-biotechnical applications, has addressed the use of experimental animal models and concluded that "an in vitro or in vivo animal model example in the specification, in effect, constitutes a 'working example' because that example 'correlates' with a disclosed or claimed method invention." The Training Materials further state that "the evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." In addition, the courts have weighed-in on the issue, concluding that a rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> ... based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

The Office Action appears to take the position that the art of gene therapy for treating cell proliferative disorders is highly unpredictable. In support of this, the Office Action cites various publications and reports that allegedly describe the state of the art of gene therapy at the time the present application was filed. In contrast to the position taken by the Office Action, reports drafted in the same, or nearly the same, time period indicate that:

> Enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human disease, and can provide important insights into human biology...accomplishments to date are impressive, and the logic of the potential usefulness of this clinical paradigm continues to be compelling. (See Crystal, Science, 270:404, 1995).

Turning to points (i) and (ii) of the Office Action, Applicants submit that one of skill in the art could readily identify, without undue experimentation, routes of administration and therapeutic dosages that would be applicable in the method of the present invention. With regard to dosage, §608.01(p) of the MPEP states that, "It is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation." The law therefore does not require recitation in a therapeutic method claim of how a vector is to be administered when a person of ordinary skill in the art could determine the most proper administration route without undue experimentation. Nevertheless, Example 9 of the present specification provide examples of transduction and intratumoral spreading of the viral

vector, including routes of administration and multiplicity of infection (MOI) calculations. One of skill in the art can easily determine the amount of vector necessary to elicit a therapeutically-effective response given that even a minimal amount of the vector will be sufficient to allow for horizontal infection of specifically targeted cells.

Relevant to point (iii), the Office Action alleges that "problems of retroviral vectors based therapies are well known in the art, particularly with regard to the delivery, the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is expressed to a degree necessary to result in a therapeutic effect" (page 18 of the Office Action). Applicants note that the vectors used in the presently claimed methods address precisely these issues. The present vector is "replication competent" and achieves transduction and expression efficiencies never achieved by previous vectors (see e.g., Example 9 and the declaration by Dr. Noriyuki Kasahara). Consequently, Applicants submit that statements contained in the Office Action regarding the "shortcomings" of current gene therapy methods may be accurate for those methods utilizing prior art vectors, but are not accurate for methods employing the RCR vectors disclosed in the present application.

As to (iv), drug resistance, the Office Action's point appears to be that a tumor may develop drug resistance to render the claimed invention ineffective. Applicants submit that just as a skilled artisan knows how to select an appropriate chemotherapy for a given cancer patient, the artisan would know how to select a proper prodrug-suicide gene combination for the claimed invention, without undue experimentation. Moreover, the Office Action cites Luqami YA (Med Princ. Pract. 14 Suppl. 1:35-48, 2005) as stating "Development of chemoresistance is a persistent problem .... Resistance ... may be inherent in a subpopulation of heterogeneous cancer cells or be acquired as a cellular response to drug exposure." Applicants submit that treating a cell proliferative disorder, such as cancer, does not require killing all the cancer cells. The partial alleviation of the symptoms of the disorder would already be relieving and desirable by the subject being treated. Thus, even if some cancer cells develop drug resistance while drug-sensitive cells are killed by the claimed method, the method successfully treats the disorder within the meaning of the claimed invention by killing the drug-sensitive cells.

It should be emphasized that even if, as asserted by the Office Action, a few parameters of the claimed invention can be optimized, this does not mean that the invention is not enabled. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ 2d 1401, 1404 (Fed. Cir. 1988). The present application, as well as knowledge available at the time this application was filed, provides sufficient direction as to how to optimize the claimed invention. Therefore, no undue experimentation would be necessary.

In summary, Applicants submit that, in light of the information contained in the present specification and in view of the level of skill in the art of gene therapy, it would not require undue experimentation to practice the invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Information Disclosure Statement

An Information Disclosure Statement with Forms PTO-1449s and Form PTO-892 was filed in the above-captioned patent application on January 11, 2002. Applicants have not yet received the Examiner's copy of the Form PTO-892, initialed to acknowledge the fact that the Examiner has considered the disclosed information.

It is respectfully requested that the Examiner initial next to each reference of the subject Form PTO-892 and return a copy to the undersigned.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5044.

Enclosed is a $125.00 check for excess claim fees and a $225.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: July 28, 2006

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